REMARKS

Entry of the foregoing, reexamination and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.116, are respectfully requested.

I. FORMAL MATTERS

A. Claim Status & Amendments

As correctly indicated in the Office Action Summary, claims 24, 25, 33-35, and 43-45 were pending in this application when last examined. The present amendment amends claims 24 and 25 to more precisely define the present invention. Support for these amendments can be found, at least, in original claims 24 and 25, and in the Specification, at least, at page 7, lines 23-28, page 11, line 5, and lines 23-24. Accordingly, no new matter is believed to have been added by this amendment.

The present amendment also cancels claims 34, 35, 44, and 45 without prejudice or disclaimer to the subject matter recited therein. Applicant reserves the right to file a continuation or divisional application directed to any of the canceled subject matter.

Thus, upon entry of the present Amendment and Reply, claims 24, 25, 33, and 43 will be pending in this application.

B. Priority Data

The objection to the Specification for allegedly not containing a reference to the priority data in the first sentence of the Specification has been withdrawn in view of the arguments set forth in the Amendment and Reply dated December 11, 2002. Nonetheless,

Applicant respectfully requests that the Examiner acknowledge the Applicant's claim for priority under 35 U.S.C. §§ 119 on the Office Action Summary form.

II. REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 24, 25, 33-35, and 43-45 remain rejected under 35 U.S.C. § 112, first paragraph, because the Specification is allegedly not enabled for the full scope of the claimed invention. See February 20, 2003 Official Action, pages 2-3, Item 7.

The Examiner believes that the Specification is enabling only for a method of treating multiple sclerosis ("MS") wherein a nucleic acid encoding a beta-interferon ("IFNβ") comprising an IFNβ secretory signal is administered to muscle cells and a pharmaceutical composition thereof, wherein the nucleic acid is DNA or naked DNA, wherein the DNA is associated with a transfection-facilitating vehicle selected from the list of cationic lipids, cationic polymers, and polypeptides suitable for injection.

Applicant respectfully traverses this rejection. Nonetheless, for the sole purpose of expediting prosecution and not to acquiesce to the Examiner's rejection, Applicant has amended the claims to the treatment of MS by administrating naked DNA encoding an IFNβ and an IFNβ secretory signal to muscle cells and a pharmaceutical composition thereof. Given that the present amendment renders the rejection moot, Applicant requests the withdrawal of this rejection.

III. REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claim 45 stands rejected under 35 U.S.C. § 112, second paragraph, as purportedly not containing antecedent basis for the limitation "said nucleic acid" in line 1. See February 20, 2003 Official Action, page 3, Item 9. The present amendment hereby cancels claim 45. Accordingly, the present amendment renders the rejection moot, and thus, Applicant requests the withdrawal of this rejection.

IV. REJECTIONS UNDER 35 U.S.C. § 102(b)

A. Croxford

Claims 25, 34, and 35 remain rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Croxford et al., THE JOURNAL OF IMMUNOLOGY, 160:5181-5187 (1998). See February 20, 2003 Official Action, pages 3-4, Item 11.

Applicant respectfully traverses this rejection for essentially the same reasons set forth in the December 11, 2002 Amendment and Reply and for the reasons set forth below.

Croxford fails to anticipate the claimed invention because the reference fails to disclose **each** and **every** element of the claimed invention. It is well established that to anticipate a claim, a single prior art reference must teach, either expressly or inherently, each and every element of the claimed invention. See M.P.E.P. § 2131; Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987); Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1379, 231 U.S.P.Q. 81, 90 (Fed. Cir. 1986).

In this case, Croxford fails to teach the treatment of MS comprising administrating **naked DNA** to muscle cells **without the use of cationic liposomses**. Instead, Croxford describes the use of a plasmid comprising the gene coding for the IFN-β **complexed with cationic liposomes** for the treatment of EAE. See Croxford, Abstract. Thus, the methods and compositions in Croxford clearly differ from the claimed invention. Nonetheless, the Examiner fails to acknowledge the above-noted differences between the teaching in the cited reference and the claimed invention. Instead, the Examiner again maintains that Croxford allegedly teaches a vector for expression of IFNβ in EAE mice and that EAE is accepted model for MS. The Examiner further asserts that the IFN protein is secreted in culture supernatant, and thus it allegedly has a secretory signal. However, no arguments have been provided to rebut the fact that Croxford fails to teach administrating **naked DNA** into muscle cells **without the use of cationic liposomses**. Since such methods and compositions clearly differ from one another, one cannot be said to anticipate the other.

Furthermore, to the extent that an attempt may be made to utilize Croxford in a subsequent obviousness rejection, Applicant notes that Croxford also fails to teach and/or suggest the claimed invention. In particular, Croxford discloses that a single i.m. injection of 100 μg of cytokine DNA (*i.e.*, naked DNA) **failed** to ameliorate the disease severity or the onset of disease. Croxford, page 5182, 2nd column, last paragraph; page 5183, Table I. This same failure was also observed when the DNA is injected **intracranially**. Croxford, page 5183, 2nd column, 1st full paragraph. Accordingly, one of ordinary skill in the art upon reading Croxford would not be motivated to use naked DNA coding for INF-β for the treatment of MS.

Thus, as the cited reference fails to teach or suggest the claimed invention, Applicant specifically requests withdrawal of this rejection.

B. Triantaphyllopous (1999)

Claims 25, 34, and 35 remain rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Triantaphyllopous et al., ARTHRITIS & RHEUMATISM, 42:90-99 (1999). See February 20, 2003 Official Action, page 4, Item 12.

Applicant respectfully traverses this rejection for essentially the same reasons set forth in the December 11, 2002 Amendment and Reply and for the reasons set forth below.

In particular, Triantaphyllopous (1999) fails to anticipate the claimed invention because the reference fails to teach **each** and **every** element of the claimed invention. As stated above, it is well established that to anticipate a claim, a single prior art reference must teach, either expressly or inherently, each and every element of the claimed invention. See M.P.E.P. § 2131; Verdegaal Bros. 814 F.2d at 631, 2 U.S.P.Q.2d at 1053; Hybritech Inc., 802 F.2d at 1379, 231 U.S.P.Q. at 90.

In this case, Triantaphyllopous (1999) differs from the claimed invention in that the reference fails to teach the treatment of MS comprising administrating **naked DNA** into **muscle cells** without the need for **lipofectin**. Instead, Triantaphyllopous (1999) teaches **intracranial** administration of a plasmid comprising the IFN-β gene for the therapy of EAE. Moreover, Triantaphyllopous (1999) administers the plasmid with **lipofectin**. See Triantaphyllopous (1999), page 257, 1st full paragraph, 1st column. Accordingly, it is clear that the method disclosed in Triantaphyllopous (1999) involves different compositions, as well as, a different route of administration. Applicant further notes that Triantaphyllopous

(1999) fails to suggest the claims amended either alone or in combination with the contemporary knowledge in the field at the time of Applicant's invention.

Similar to the previous rejection, the Examiner fails to acknowledge the above-noted differences between the teaching in the cited reference and the claimed invention. Instead, according to the Examiner, Triantaphyllopous (1999) teaches a method for the introduction of INF-β expression vectors into EAE mice. The Examiner also asserts that the IFN protein is secreted in culture supernatant, and thus it has a secretory signal. However, again, no arguments have been provided to rebut the fact that Triantaphyllopous (1999) teaches different compositions, as well as, a different route of administration.

Thus, as the cited reference fails to teach or suggest the claimed invention, Applicant specifically requests withdrawal of this rejection.

C. **Triantaphyllopous (1998)**

Claims 25, 34, and 35 remain rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Triantaphyllopous et al., GENE THERAPY, 5:253-263 (1998). See February 20, 2003 Official Action, page 4, Item 13.

Applicant respectfully traverses this rejection for essentially the same reasons set forth in the December 11, 2002 Amendment and Reply and for the reasons set forth below.

Triantaphyllopous (1998) fails to anticipate the claimed invention because the reference fails to disclose **each** and **every** element of the claimed invention. Again, as stated above, it is well established that to anticipate a claim, a single prior art reference must teach, either expressly or inherently, each and every element of the claimed invention.

See M.P.E.P. § 2131; Verdegaal Bros., 814 F.2d at 631, 2 U.S.P.Q.2d at 1053; Hybritech Inc., 802 F.2d at 1379, 231 U.S.P.Q. at 90.

In this regard, Triantaphyllopous (1998) fails to teach the treatment of MS comprising administrating **naked DNA** into **muscle cells**. Instead, Triantaphyllopous (1998) describes **intracranial injection** of **transfected fibroblasts** expressing IFN-β to treat collagen induced arthritis in mice. See Triantaphyllopous (1998), Abstract. Thus, Triantaphyllopous (1998) describes different compositions (*i.e.*, fibroblast cells versus naked DNA), as well as, a different route of administration (*i.e.*, intracranial injection versus injection into muscle cells). Applicant further notes that Triantaphyllopous (1998) fails to suggest the claims as-amended either alone or in combination with the contemporary knowledge in the field at the time of Applicant's invention.

Once again, the Examiner fails to acknowledge the above noted differences between the teaching in the cited reference and the claimed invention. Instead, the Examiner maintains that Triantaphyllopous (1998) teaches a vector for expression of IFNβ expression and a method for introducing the vector into EAE mice. However, this position fails to provide arguments to rebut the fact that Triantaphyllopous (1998) teaches different compositions, as well as, a different route of administration. Moreover, this rejection directly contradicts the position taken in the subsequent rejection under 35 U.S.C. § 103 wherein it is indicated that Triantaphyllopous (1998) "does not teach the treatment of MS by administering naked DNA expressing beta-interferon into a patient." See February 20, 2003 Official Action, page 5, Item 15, last sentence. Thus, as acknowledged by the Examiner, Triantaphyllopous (1998) fails to teach the claimed invention.

Therefore, as the cited reference fails to teach or suggest the claimed invention, Applicant specifically requests the withdrawal of this rejection.

V. REJECTION UNDER 35 U.S.C. § 103(a)

Claims 24, 25, 33-35, and 43-45 stand rejected under 35 U.S.C. § 103(a) as purportedly obvious over Triantaphyllopous (1998) in view of Youssef et al., THE JOURNAL OF IMMUNOLOGY, 161:3879 (1998) and Felgner et al., U.S. Patent No. 5,580,859. See February 20, 2003 Official Action, pages 5-6. This is a new grounds of rejection.

Applicant respectfully traverses this rejection for the reasons set forth below.

The rejection fails to set forth a *prima facie* case of obviousness against the claimed invention because the cited references fail to provide the requisite suggestion and/or motivation for one of ordinary skill in the art to combine and/or modify the references to arrive at the claimed invention with a reasonable expectation of success. To establish a *prima facie* case of obviousness, three criteria must be met. First, the prior art references must teach or suggest each and every element of the claimed invention. See M.P.E.P. § 2143.03; In re Royka, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974); In re Zurko, 111 F.3d 887, 888-89, 42 U.S.P.Q.2d 1476, 1478 (Fed. Cir. 1997); In re Wilson, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970).

Second, there must be some suggestion or motivation in the references to either modify or combine the reference teachings to arrive at the claimed invention. See M.P.E.P. § 2143; In re Vaeck, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991). This element requires that an objective teaching in the prior art or that knowledge generally

available to one of ordinary skill in the art that would lead that individual to combine the relevant teachings of the references. In re Fine, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988). In other words, the Examiner must provide a logical reason as disclosed in the prior art at the time of the invention for combining the references along the lines of the invention; otherwise the use of such teachings as evidence of non-obviousness will entail impermissible hindsight. Ex parte Stauber and Eberle, 208 U.S.P.Q. 945, 946 (Bd. App. 1980).

Third, the prior art must provide a reasonable expectation of success. See M.P.E.P. § 2143.02; Vaeck, 947 F.2d at 488, 20 U.S.P.Q.2d at 1438; In re Merck & Co., Inc., 800 F.2d 1091, 231 U.S.P.Q. 375 (Fed. Cir. 1986).

As discussed above, Triantaphyllopous (1998) describes the **intracranial** injection of **fibroblasts** expressing IFN-β to treat collagen induced arthritis in mice. See Triantaphyllopous (1998), Abstract. Fibroblast cells and intracranial injection clearly differ from naked DNA and intramuscular injection as evidenced by the Examiner's statement that Triantaphyllopous (1998) "does not teach the treatment of MS by administering naked DNA expressing beta-interferon into a patient." See February 20, 2003 Official Action, page 5, Item 15, last sentence. Thus, Triantaphyllopous (1998) fails to teach and/or suggest administrating **naked DNA** into **muscle cells** to treat MS.

The Examiner relies on Yousset as allegedly teaching that DNA vaccination with chemokines is useful for treating Experimental Autoimmune Encephalomyelitis ("EAE") in mice and that DNA vaccination is useful for expressing foreign antigens. The Examiner relies on Felgner as allegedly teaching that it was routine in the art to directly administer

naked DNA molecules to tissues for providing a therapeutic protein for treating diseases. However, It is well established that a prior art teaching must be considered as a whole including portions that "teach away" from the claimed invention. See M.P.E.P. § 2141.02; W.L. Gore & Associates, Inc., v. Garlock, Inc., 721 F.2d 1540, 220 U.S.P.Q. 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984). In this regard, Youssef teaches that MIP1α and MCP1 are involved in the initiation of EAE. Youssef, page 3877, 2nd column, lines 1-9. Moreover Youssef discloses that vaccination against MIP1α and MCP1 by direct injection into muscle cells of a naked DNA encoding these proteins, leads to the production of an anti-MIP1α and anti-MCP1 immune response which protected injected rats from EAE. See Youssef, page 3877, Abstract.

Thus, one skilled in the art, upon reading Triantaphyllopous (1998), would have believed that the production of IFN β in the central nervous system leads to protection against EAE. Also, upon reading Youssef and Felgner, the skilled artisan would have thought that the injection into muscle cells of naked DNA coding for a protein leads to an immune response against the encoded protein. Therefore, one skilled in the art would have thought that intramuscular injection of a naked nucleic acid encoding IFN-β would lead to the production of an immune response against IFN-β. Such an immune response was believed to induce the neutralization of the protein in the central nervous system (Youssef, page 3877, 2nd column, lines 49-54) which contradicts the need to increase the production of IFN-β as disclosed by Triantaphyllopous (1998). Consequently, one of ordinary skill in the art would not be motivated inject naked DNA encoding IFN-β into the muscle cells for the purpose of treating MS.

Furthermore, Croxford further corroborates this lack of motivation to combine. As discussed previously, Croxford discloses that a single i.m. injection of 100 μg of cytokine DNA (*i.e.*, naked DNA) **failed** to ameliorate the disease severity or the onset of disease. See Croxford, page 5182, 2nd column, last paragraph; page 5183, Table I. This same failure was also observed when the DNA is injected **intracranially**. Croxford, page 5183, 2nd column, 1st full paragraph. Accordingly, since Croxford taught that i.m. injection of naked DNA failed to ameliorate disease severity, one of ordinary skill in the art upon reading Croxford would not have been motivated to use naked DNA encoding INF-β for the treatment of MS. There simply was no reasonable expectation of success for doing so.

Therefore, since the combination of Triantaphyllopous (1998) in view of Youssef, and Felger does not teach or suggest each and every element of the claimed invention and because there is no motivation to combine these references to arrive at the present invention with a reasonable expectation of success, Applicant submits that the cited references do not and indeed cannot render the claimed invention obvious. Thus, for at least these reasons, Applicant respectfully requests the withdrawal of the rejection of claims 24, 25, 33-35, and 43-45 under 35 U.S.C. § 103(a).

CONCLUSION

From the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order, and such action is earnestly solicited.

In the event that there are any questions relating to this Amendment and Reply, or to the application in general, the Examiner is invited to telephone the undersigned concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By: _____
Jay F. Williams
Registration No. 48,036

P.O. Box 1404
Alexandria, Virginia 22313-1404
(703) 836-6620

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